SOMATOSTATIN ANALOGUES IN THE MANAGEMENT OF BENIGN INSULINOMAS

Z. LARON

Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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In this issue of the ISRAEL JOURNAL OF MEDICAL SCIENCES, Glaser et al. (1) describe the successful treatment of a 39-year-old patient with a suspected benign small insulinoma by continuous s.c. infusion of the somatostatin analogue SMS 201-995 (Sandostatin®, Sandoz, Switzerland). This case report raises a few interesting questions relating to the usefulness of somatostatin and its analogues in the treatment of insulinomas.

Insulinomas are uncommon tumors occurring at any age, but are most often diagnosed in the fourth to sixth decade of life and with an equal sex distribution. Approximately 75% of insulinomas are small, benign, single adenomas of less than 3 cm in diameter that function autonomously. Ten percent of insulinomas occur as multiple benign adenomas scattered throughout the pancreas, and another 10% appear as malignant β-cell carcinomas that are usually larger in size than the benign tumors (2).

Somatostatin is a peptide synthesized by several tissues and circulates in several forms: a 14 amino acid sequence found mainly in the blood and a 28 amino acid form secreted predominantly in the gastrointestinal tract. It can act as a neurotransmitter, a systemic hormone (endocrine function), or a local hormone (paracrine function). It inhibits the secretion of growth hormone, thyroid-stimulating hormone, glucagon and insulin (3), as well as gastrin and pancreatic polypeptide. Its insulin-suppressing effect has induced clinicians to attempt using it in the treatment of insulin-secreting tumors, i.e., insulinomas. However, its very short half-life of 2 min made it impractical for clinical use when not given in continuous infusion. A major advancement was the synthesis of a small (8 amino acid) somatostatin analogue, i.e., the octapeptide octreotide (Sandostatin) (4). Since this drug has a biological half-life of 90-120 min (5), it can be given several times a day when administered s.c. Subcutaneous injections of 50-100 μg result in plasma concentrations of 2-4 μg/l (6). The clinical effects peak approximately 2 h after administration, but there is some variability depending upon the target tissue; thus the thyrotrophin-releasing hormone suppression is greater than that of growth hormone. Short-term use of SMS 201-995 in healthy individuals (5,7) produces a suppressive effect on the stimulated secretion of thyroid-stimulating hormone and human growth hormone, and a suppression of basal levels of glucagon and insulin.

The above findings led to a series of clinical trials, which evaluated the possible clinical application of this new drug for treating pituitary and gastrointestinal tumors, and even non-neoplastic diseases of the gut (6,8,9). These studies found that SMS 201-995 is sometimes a lifesaving or life-prolonging means of treatment. However, the discussion below will refer only to the treatment of benign insulinomas, the most frequent hypoglycemia-causing pancreatic tumor. A recent paper (6) reviewed the use of SMS 201-995 in eight patients with benign insulinomas who were treated for relatively short periods of time. In all eight patients the drug was given by repeated daily s.c. injections. The conclusions drawn were that the effects of SMS 201-995 on plasma insulin and blood glucose were variable. In some patients SMS 201-995 did not improve the hypoglycemia. The innovation in treatment reported by Glaser et al. (1) is the use of an external pump that delivers the drug by continuous s.c. infusion.

Address for correspondence: Dr. Z. Laron, Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, POB 85, 49100 Petah Tikva.

This mode of drug administration appears to be the cause of the excellent therapeutic results obtained; however, additional cases are needed to confirm this supposition.

Because benign insulinoma is primarily a single tumor, surgery is usually the therapy of choice. Nevertheless, the patient described by Glaser et al. (1) demonstrates that surgery is not always simple and/or successful. Thus, somatostatin octreotide analogue (Sandostatin; SMS 201-995) may be indicated both as a preoperative treatment of benign insulinoma and as the long-term treatment of choice for inoperable patients.

A few words of caution are in place. Octreotide, like somatostatin-14, almost completely suppresses postprandial insulin release, thereby rendering a patient diabetic (10). Careful dose adjustment in long-term treatment should prevent this undesirable effect; its occurrence is probably diminished by the concomitant suppression of glucagon and growth hormone.

Rebound secretion of insulin, growth hormone, or gastrin reported after cessation of somatostatin infusion (11,12), does not seem to be a major drawback of SMS 201-995. However, because somatostatin decreases pancreatic secretion and gallbladder contractibility, malabsorption, steatorrhea and gallbladder stones may occur (6,13). Patients receiving long-term SMS 201-995 therapy should be examined periodically for these side effects.

In conclusion, somatostatin analogues, such as Sandostatin and possibly others with a more prolonged action to be developed, are a useful therapeutic addition in the treatment of pancreatic tumors including benign insulinoma. This view is more optimistic than that recently expressed by Maton (6), and is based on the fact that insulin modulation of benign insulinomas may differ from that of malignant insulinomas, and that continuous s.c. infusion may be superior to repeated daily injections, which lead to incomplete suppression and rebound secretion of hormones.

Z.L. is the incumbent of the Irene and Nicholas Marsh Chair of Endocrinology and Juvenile Diabetes.

REFERENCES

1. Glaser B, Rosler A, Halperin Y. Chronic treatment of a benign insulinoma using the long acting somatostatin analogue SMS 201-995. *Isr J Med Sci* 1990;**26**:16-19.
2. Smith RJ. Hypoglycemia. In: Marble A, Krall LP, Bradley RF, Christlieb AR, Soeldner JS, eds. Joslin's diabetes mellitus, 2nd ed. Philadelphia: Lea & Febiger, 1985:867-881.
3. Reichlin S. Somatostatin. *N Engl J Med* 1983;**309**:1495-1501, 1556-1563.
4. Bauer W, Briner U, Doepfner W, et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci* 1982;**31**:1133-1140.
5. Kutz K, Nuesch E, Rosenthaler J. Pharmacokinetics of SMS 201-995 in healthy subjects. *Scand J Gastroenterol* 1986;**119**(Suppl 21):65-72.
6. Gorden P, moderator. Somatostatin and somatostatin analogue (SMS 201-995) in treatment of hormone secreting tumors of the pituitary and gastrointestinal tract and non-neoplastic diseases of the gut. *Ann Intern Med* 1989;**110**:35-50.
7. Davies RR, Miller M, Turner SJ, et al. Effects of somatostatin analogue SMS 201-995 in normal man. *Clin Endocrinol* 1986;**24**:665-674.
8. Lamberts SW. Non-pituitary actions of somatostatin. A review on the therapeutic role of SMS 201-995 (sandostatin). *Acta Endocrinol [Suppl] (Copenh)* 1986;**276**:41-55.
9. Lamberts SWJ. Somatostatin analogs in the management of gastrointestinal tumors. *Horm Res* 1988;**29**:118-120.
10. Bloom SR, Polak JM. Somatostatin. *Br Med J* 1987;**295**:288-289.
11. Laron Z, Pertzelan A, Doron M, Assa S, Keret R. The effect of dihydrosomatostatin in dwarfism with high plasma immunoreactive growth hormone. *Horm Metab Res* 1977;**9**:338-339.
12. Buck M, Kvols LK, O'Dorisio TM. Rebound hypergastrinemia after cessation of a somatostatin analogue (SMS 201-995) in malignant gastrinoma. *Am J Med* 1987;**82**:92-95.
13. Kvols LK, Buck M, Moertel CG, et al. Treatment of metastatic islet cell carcinoma with a somatostatin analogue (SMS 201-995). *Ann Intern Med* 1987;**107**:162-168.

TREATMENT OF AIDS WITH AL-721

AVRAHAM KLAJMAN

Department of Medicine A, Meir General Hospital, Kfar Saba, Israel

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The acquired immunodeficiency syndrome (AIDS) was first described in the United States in 1981. It has been estimated that the total number of AIDS cases in the USA will reach or exceed 270,000 by the year 1991, with infected people exceeding a million and a

Address for correspondence: Dr. A. Klajman, Department of Medicine A, Meir General Hospital, 44281 Kfar Saba.